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Method For The Continuous Production Of Hydrolytically Broken  
Down And Possibly Substituted Starch, Use Of Hydrolytically  
Broken Down Starch And Device For Producing Same

Description

Method for the continuous production of hydrolytically broken down starch or hydrolytically broken down substituted starch products.

The invention concerns a method for the production of hydrolytically broken down starch or hydrolytically broken down substituted starch products, such as hydroxyethyl starch or hydroxypropyl starch, use of the products produced according to the invention in the medical field, in particular as plasma diluent, as well as a device for producing hydrolytically broken down starch or hydrolytically broken down substituted starch products.

It is known to hydrolytically break down starch and substituted starch products, such as hydroxyethyl or hydroxypropyl starch. Thus, a method for producing a starch hydrolysate is described in DE-OS 30 000 465 in which  $\alpha$ -amylase is used. The method described there works in a very complicated manner and can not easily be carried out in a continuous manner. Moreover, it can only be applied to a limited degree.

A method is also described in DE-A1 33 13 600 for the hydrolytical breakdown of starch in which  $\alpha$ -amylase, beta-amylase or pullulanase is used, whereby the starch can be

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substituted, for example, with ethylene oxide before or after the hydrolysis.

The breakdown of hydroxyethyl starch to form a product that can be used as a plasma expander is described, *inter alia*, in EP-A1 0 402 724.

Transferring methods of this type to a continuous scale is not easily possible. Therefore, there is a need for a continuous method that works economically and that results in products that can be used in a variety of fields.

As is known, high demands are made on just those products which are used in the medical field. On the one hand, products are required that do not cause any allergies in the patient, on the other hand, the breakdown rate, i.e. the decrease in concentration within the first 24 hours, should be very high in the patient and the organ half-life short. Moreover, the clinical use of broken down starch products depends quite heavily on the physical chemical properties. In this connection, reference is made to the articles of Klaus Sommermeyer et al. that were published *inter alia* in Krankenhauspharmacie 8, (8271/8) (1987) and starch/Stärke 44 (5), 173-9 (1992).

The object of the invention is to provide a method for the continuous production of hydrolytically broken down starch or hydrolytically broken down substituted starch products that works economically, with which the properties of the breakdown products can be set selectively, carried out with slight apparatus-related and method-related assembly and which results in products that can be used especially in the medical field and in food technology.

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This object is solved by a method according to claim 1. Further advantageous embodiments of the method according to the invention are described in claims 2 to 9.

A further object of the invention is the use of the products produced according to a method as per claims 1 to 9 as a plasma diluent or to produce dialysis solutions. A further object of the invention is a device for carrying out a method for the continuous production of hydrolytically broken down starch derivatives according to claims 11 to 13.

To carry out the method according to the invention, ordinary starches can be used such as, for example, potato starch, wheat starch, cassava starch and the like. The starches rich in amylopectin are especially suitable, such as the wax-like milo (SORGHUM) starch, corn starch or rice starch. The starches can be used modified or not modified; the starch can also be used as an already partially broken down starch. In particular, hydroxypropyl and preferably hydroxyethyl starch are used as modified starches.

The modification can be carried prior to hydrolysis, yet also after hydrolysis. Preferably, however, it is modified, in particular ethoxylated, prior to hydrolysis.

The modified or non-modified starch to be broken down is advantageously used as an aqueous solution or suspension, whereby suspension is understood to also mean grains containing starch and found in water. The concentration of starch or modified starch in the solution or suspension can be adjusted within broad limits.

The concentration can already be set prior to hydrolysis with

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respect to the desired intended use of the end product: furthermore, it is possible to influence the property profile of the end product by selecting the concentration in combination with further parameters such as hydrolysis temperature, dwell time etc. Preferably, the concentration is 25 - 30 % by weight relative to the total weight.

After mixing with a hydrolyzation agent, in particular a mineral acid such as hydrochloric acid, it is heated or cooled to the desired temperature, preferably with the aid of heat exchangers.

The suspension or solution is then conveyed to a tubular tempered reactor, whereby reactor is understood to also be a plurality of reactor units which are arranged in tandem. The reactor is tempered to the desired hydrolysis temperature, preferably to 70 - 80°C. The product to be hydrolyzed is fed to the tubular reactor from the bottom i.e. against the force of gravity, so that the suspension or solution moves from the bottom to the top, i.e. in ascending direction. If several reactor units are used, all reactor units are aligned in parallel and are each flowed into from the bottom.

In principle, it is possible to carry out the predominant part of the hydrolysis in a single tube. However, several tubular reactor units can also be arranged in a row, for example, be arranged beside one another or above one another, as is preferred for production and handling reasons. The conveyance of the hydrolysis product from one reactor unit into the next reactor unit can be accomplished in a simple manner, e.g. with pipe connections, perhaps also by inserting an adjustable pump.

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The tube reactors are laid out in such a manner or the flow velocity measured such that at least a predominant part of the hydrolysis, i.e. at least 60 %, preferably 85 - 95 % of the breakdown takes place in the tubular tempered reactors. Thus, this breakdown preferably takes place as a first step in the form of a rough breakdown - as will be described below. The tubular reactors preferably contain no mixing elements at all so as to ensure a uniform forward movement of the suspension during hydrolysis without mixing. Sampling points can be provided on the connecting pipes.

The product already broken down for the most part, e.g. up to 90 %, can then be conveyed to one or more further reactors in which the hydrolytical breakdown is carried out to the desired extent (second step in the form of a fine breakdown). Preferably, the remainder of the hydrolysis in the fine breakdown step is carried out in reactors that have static mixing elements.

With aid of the reactor units, it is possible to conduct the hydrolysis up to a preset final value and to fine tune the method. Therefore, advantageously, these reactors are also provided with means for controlling the temperature. In this way, it is possible to accurately set the degree of hydrolysis. The degree of hydrolysis is preferably tested with aid of viscosity measurements.

According to the invention, it is preferable to carry out a two-step continuous breakdown process, consisting of a rough and fine breakdown. On the other hand, however, a one-step breakdown method can also be carried out corresponding to the rough breakdown when the hydrolytic breakdown does not by necessity have to result in an exact preset degree of

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breakdown, but can fluctuate within set limits.

The flow of the liquid product to be hydrolyzed against the force of gravity has the advantage that the layers of the solution/suspension found in a reactor virtually do not mix. Due to the hydrolysis, amylolysis products having a decreasing chain length are continuously formed, the result of which is that the liquid layers have an ever lower viscosity, seen from the bottom of the reactor to the top. In the reactor, therefore, there are layers having a continuously decreasing drop in viscosity - seen from the bottom to the top against the force of gravity.

During hydrolysis, the solution to be treated is moved through the reactor at such a speed that enables an essentially undisturbed formation of this viscosity profile. After the reactor length, i.e. the reaction length during the continuous method, has been fixed, the conveying speed establishes the total reaction time which is determined in dependence on the selected degree of hydrolysis.

If a multiple tube reactor installation is used, then the connecting pipes are measured in such a way in their cross section that the layers having the same viscosity can flow from the one to the other reactor essentially without disturbance, i.e. without the layers mixing, so that the hydrolysis treatment can take place in the next reactor unit against the force of gravity.

The property profile of the hydrolysate obtained can also be influenced by the selection of the concentration of the initial solution or initial suspension as well as the molecular weight of the starch or starch derivative used, the

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The method according to the invention offers a substantial



simplification of the hydrolysis process and thus results in considerable savings in costs since only special steels (e.g. HASTELLOY) can be used for acid hydrolysis processes, which is quite expensive for equipment provided with static mixers.

It is possible to produce a hydrolysis product with specific properties in a selective and reproducible manner with the method of the invention. Thus, exactly defined final values such as molecular weight, molecular weight distribution, degree of substitution and the like can be set. These values can be constantly obtained in a reproducible manner for a long period, while in the so-called batch operation the fluctuations are very great and difficult to control. This not only applies to the breakdown of the starch, but also for the breakdown of modified products, so that, in combination with a modification process for the various intended purposes, it is possible to produce preparations having the desired properties.

The method is very flexible and can be automated to a great extent.

The method according to the invention can be carried out with an installation as schematically shown in the drawing.

A device for the continuous hydrolysis of starch or starch derivatives is indicated with 10 in the drawing. A hydroxyethyl starch solution is continuously fed to a mixer/heat exchanger 14 from station 12, said mixer/heat exchanger 14 being connected with a container 16 that has e.g. hydrochloric acid as a hydrolyzation agent. A pH value is set at 1-2 in the mixer/heat exchanger 14 and the solution is tempered to a preselected hydrolysis temperature, e.g. 70 -

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80°C.

The hydrolysis solution is then conveyed by means of a pump 18 having a preset pump rate, via a first conduit 20 to a reactor 22 (according to the drawing, three reactor units 24 - 28) as reaction stage (main or rough hydrolysis station) in such a way that the hydrolysis solution rises against the force of gravity from the bottom to the top, as is shown by the direction of the arrows in the reactor units 24 - 28. For this purpose, the reactor unit 24 has, when in operation, an inlet tube 23 arranged at the bottom and an outlet tube 25 arranged at the top. These tubes 23 and 25 are provided in the same way in the remaining reactor units 26 and 28. The conduit 20 is thereby dimensioned in such a way in its cross section that each of the hydrolysis layers arriving from the reactors 24 - 28 cannot essentially intermix.

On the other hand, however, it can also be sufficient that only one reactor unit 24 is used as main hydrolysis station (shown with 22 in a broken line), to the extent that it is adequately dimensioned in its volume. It is thereby essential to the invention that the slowly rising hydrolysis solution does not intermix in its layers, i.e. the individual layers with their various states of hydrolysis should not intermix, similar as the bases during fractionated distillation. As a result, a solution having a defined degree of hydrolysis can be drawn off in each case at the upper outlet point of the reactor units 24 - 28, whereby the hydrolysis can then be finely set. The reactor units 24 - 28 are therefore designated as main hydrolysis station. In particular, the reactor units 24 - 28 are not furnished with mixing elements on the inside which could cause the entire hydrolysis solution to be intermixed. Therefore, the hydrolysis gradient which is

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correlated with the viscosity of the individual layers should remain essentially unchanged, i.e. the individual layers should not mix with one another.

Advantageously, the reactor units 24 - 28 have a tempering jacket 27 as shown symbolically in the reactor unit 26 in the drawing. This tempering jacket is flowed through by a tempering liquid, usually water, maintained at a preset temperature and thus maintains the contents of the respective reactor units 24 - 28 at the desired temperature. The latter is determined in each case thereby that liquid samples are removed at specific points on the reactor units 24 - 28 to determine the respective viscosity, i.e. the respective degree of hydrolysis, and that the final degree of hydrolysis is determined herefrom with reference to tables and the known conveying rate.

The reactor units 24 - 28 are dimensioned in such a way that a minimum flow rate is ensured at a preset viscosity to prevent an intermixing of the respective layers due to diffusion. The latter essentially depends *inter alia* on the viscosity. Thus, the lower limit of the flow rate is at about 3 cm/min, if the viscosity of the solution to be hydrolyzed is at about 20 mPa x s. Advantageously, the flow rate is between 5 - 20, especially between 10 - 15 cm/min.

The length/diameter ratio of the reactor units 24 - 28 is also determined by the throughput of the solution to be hydrolyzed. Advantageously, this ratio is between 10:1 to 20:1.

Advantageously, the main hydrolysis station 22 is connected with a fine hydrolysis station 32 (shown by a broken line) by means of a second conduit 30, as shown by the reactor units 34

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- 40. These reactor units 34 - 40 are advantageously connected with a tempering unit 42, for example, by a tempering jacket, through which a tempering liquid flows that is maintained at a preset temperature and which corresponds to the tempering jacket 27. The temperature that is advantageous for the hydrolysis can be set herewith, said temperature being advantageously monitored and controlled by means of the viscosity setting in the hydrolysis solution. Moreover, these reactor units 34 - 40 are furnished with mixing elements 44 (shown schematically) so that a uniform intermixing takes place in the reactors to ensure a uniform hydrolysis. The tempering unit 42 is only shown in the drawing in connection with the reactor unit 34 and can, of course, also be provided in the other reactor units 36 - 40. Similarly, it is fed from a standard tempering liquid source (not shown).

For example, a hydrolysis of up to 95 % can take place in the main hydrolysis station 22, while only 5% of the desired degree of hydrolysis are obtained in the fine hydrolysis station 32.

As noted above, according to the invention, the fine hydrolysis station 32 does not have to be provided, since a hydrolysis product having a dense molecular weight distribution is produced there. If a dense distribution of this type is not required, then a fine hydrolysis station 32 of this type can be omitted.

As shown in the drawing, the liquid to be hydrolyzed is advantageously also conveyed from the bottom to the top in the fine hydrolysis station 32 in order to substantially eliminate the effects of the force of gravity.

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To stop the hydrolysis, the solution is mixed with a caustic soda, conveyed from the storage vessel 48, in a neutralization station 46 at the end of the hydrolysis. In this respect, the container 46 is connected to the fine hydrolysis station 32 with a third conduit 50.

The mixture is then conveyed for further treatment, e.g. diafiltration and spray drying, from the vessel 46 to further treatment apparatus (not shown).

The invention will be explained in further detail by the following example.

#### Example 1

A 30% starch solution is produced by adding water and lye. Hydroxyethyl starch having a molecular weight of 1.4 million daltons is produced therefrom in a continuous starch ethoxylating installation by means of ethylene oxide and conveyed to a tube reactor without mixing elements at a volume flow of about 11.3 l/h. The reactor is dimensioned about 2.6 m x DN 100. The ethoxylation is not an object of the invention since a starch can also be used for the subsequent hydrolysis.

0.2 l/h 25% HCl is added to the hydroxyethyl starch solution in doses prior to being introduced into a hydrolysis reactor; furthermore, the reaction solution is brought to a temperature of 70°C by means of a heat exchanger, whereby the pH value is brought to about 1.0. The hydrolysis reactor is maintained at 70°C by means of tempering, whereby it is essential that the untreated solution flow through the reactor, which does not

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have mixing elements, from the bottom to the top (against the force of gravity). The dwell time of the solution is approximately 2 hours. The molecular weight was thereby reduced from 1.4 million to 300,000 daltons.

In a fine hydrolysis part, advantageously connected in tandem and consisting of several reactors having static mixing elements, a final molecular weight (weight means) of approximately 250,000 daltons is set. The hydrolysis is then ended by means of neutralization. The mixture is then purified by means of diafiltration with aid of a membrane to an exclusion limit of 50,000 daltons. The dried product is extremely suitable as a plasma diluent.

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